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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,682	04/28/2000	DAVID J. FITZGERALD	015280-31010	5396

7590 05/01/2006

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EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,682	FITZGERALD, DAVID J.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-18 and 47-58* is/are pending in the application.

4a) Of the above claim(s) *4-6,11 and 14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,8,12,13 and 47-58* is/are rejected.

7)☒ Claim(s) *52-56* is/are objected to.

8)☒ Claim(s) *4-6,11 and 14-18* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 7-8, 12-13, 47-50 and new claims 51-58 are under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

1. ***Claim Objections*** Claim 47 objected for depending from withdrawn claim 15 has been obviated through amending claim 47 to depend from claim 1.
2. ***Withdrawn Claim Rejections - 35 USC § 112*** Claims 1, 3,7, 12-13, 47-50 rejected under 35 U.S.C. 112, second paragraph, in subparagraph (2), for reciting the term **subsequence** has been obviated through claim amendment to delete this term.
3. Claims 1-3,7-8,12-13,47-50 rejected under 35 U.S.C. 112, second paragraph, for defining the epitope region to contain 5 to 350 amino acids, but redefined to "consisting essentially of one cysteine to cysteine disulfide bonded loop" which is only two amino acids, has been obviated through amending the claims to recite the phrase "one cysteine-cysteine loop".
4. Claim 47 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been obviated through amendment of claim 47 to depend from claim 1.
5. Claims 49-50 rejected under 35 USC 112, second paragraph for reciting the limitation "the cell" in an effort to further limit the immunogenic of claim 1, but claim 1 does not comprise a cell, but a cell recognition domain which is only a portion of a cell, has obviated by amending claims 49-50 to recite the term mammal that is recited in claim 1.

Response to Arguments

6. Applicant's arguments filed December 21, 2005 have been fully considered but they are not persuasive.

7. ***Rejections Maintained*** : The rejection of amended claims 1-3, 7-8, 12-13, 47-50, 51-58 as previously applied to claims 1 and 47, under 35 USC 112,first paragraph written description is traversed on the grounds that the instant Specification discloses at page 27, lines 21-22 that amino acids 339 and 343 appear to be necessary for translocation and at page 26,and 27 of the Specification the essential subject matter pertaining to domain II sequence variants is disclosed.

8. It is the position of the examiner upon reconsideration of the disclosure at pages 26-27 of the instant Specification, that at page 27 specific amino acid sequences from Domain II of PE can be deleted, specifically amino acids 253-279 and 345-364, but teaches that the domain should "minimally contain, e.g., amino acids 280-344 of domain II of PE (page 27, paragraph 2)".

This species does not provide original descriptive support for the highly variable genus of translocation domains that are defined by the phrase "having an amino acid sequence at least 95% identical to the sequence of Pseudomonas aeruginosa A (PE) (SEQ ID NO 2) from amino acid position 280 to amino acid position 344".

The species defined in the Specification at page 27, paragraph 2 does not evidence any changes from PE domain II amino acids 280-344, but what is claimed is a domain containing a sequence that shares 95% amino acid identity to PE domain II amino acids 280-344.

Pictorially, the scope of what is now claim is shown below.

Instant Spécification, page 27: 280-344 ----------

(aa that shares 100% identity but comprises other amino acids that differ) ↓

Claim 1 : an amino acid sequence that is 95% identical to 280-344 : XXXX --XXXXXXXXXXXXXXXX

(translocation activity from another source not specified).

---- identical amino acids; X: amino acids that differ from the reference sequence

Page 27 teaches that specific amino acids must be conserved and are critical to maintaining translocation activity. The critical amino acid positions may be changed based upon the combination of claim limitations recited in the claims. The highly variable genus has not been described. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. All positions may be mutated based upon the combination of claim limitations recited in the claims, as long as the sequence maintains 95% identity to an amino sequence of SEQ Id NO 2. Applicant's arguments directed to positions that are not to be mutated verses specific positions that can be mutated are not commensurate in scope with the instantly claimed invention . A genus of polypeptide translocation domains of the recited degree of variation has not been disclosed, nor described in such a way that one of skill in the art would have known that Applicant was in possession of the claimed invention at the time of filing for the instant invention.

While the independent claim has been amended to no longer recite the term "subsequence" of the polypeptide amino acid sequence for the translocation domain, the claim still encompasses an amino acid sequence that is not limited to sequences from Pseudomonas aeruginosa exotoxin A, amino acids 280-344. The combination of claim limitations has not been described, because the overall sequence of the polypeptide has only been defined by function and not structure, and while the sequence portion is structurally defined with reference to a range of amino acids 280-344 of SEQ ID NO 2, the claimed genus of variants with any type of changes at any position within this range (280-344 of SEQ ID NO 344) has not been described, nor evidences original descriptive support, in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. Applicants further traverse that the Specification teaches that amino acids at positions 339 and 343 appear to be necessary for translation, that procedures for making variants of SEQ ID NO 2 are conventional in the art and were well established at the time of filing.

10. It is the position of the examiner that the rejection was not a scope of enablement, but written description over a highly variable genus based upon a single species which does not vary from the reference amino acid sequence range. Possession of an invention at the time of filing is not defined by a method of making and testing variants in the future. Possession of the highly variable genus has not been described in such a way that one of skill in the art would have known that Applicant was in possession of the claimed invention at the time of filing for the instant invention.

11. Applicant cites a reference to Kasturi et al (1992) that shows alanine substitutions at 19 positions in Exotoxin A domain II from positions 280-344 and found 16 to retain at least some activity.

12. It is the position of the examiner that the claimed changes for domain II is not limited to substitution of alanine into positions 280-344. Applicant's traversal is not commensurate in scope with the instantly claimed invention as now claimed.

13. Applicant points to Example 14 of the Office's written description guidelines which specifically concerns a hypothetical invention claiming a protein having at least 95 % sequence homology to the disclosed sequence of the solely exemplified protein and the biological activity of the disclosed protein.

14. It is the position of the examiner that that language of Example 14 and the claimed invention are not the same. What is now claimed need only comprise ***an amino acid sequence*** **of 280-344 that shares 95% (98% identity, claim 47) identity** ***to this sequence*** and evidences translocation activity, while Example 14 requires that variants to be ***95 % identical to the entire SEQ ID NO*** and does not recite the term "homolog" as asserted by Applicant.

15. ***Claim Rejections - 35 USC § 102 Maintained:*** The rejection of claims 1, 7-8,12,47-50, 51, 52, 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Cardy et al (US 2002/0106370, effective filing date May 15, 1995) in light of evidence provided by US Pat. 6,303,120: is traversed on the grounds that: Cardy et al do not disclose or suggest a cell recognition domain which binds to an epithelial cell surface receptor on the apical surface of a mucosal membrane of a mammal.

16. It is the position of the examiner that Cardy et al at paragraphs [0011, "on any cell type"], [0014 "mucosal cells"], [0038, "Lewis-Y"] [0042-0043, administered to mucosal surface], discloses the immunogenic composition to bind to mucosal cells, as it is administered to a mucosal surface for stimulation of an immune response. US Pat. 6303120 provides evidence that Lewis Y antigen is expressed on epithelial cells (see claim 4).

Therefore, Cardy et al inherently anticipates the instantly claimed invention in light of the fact that the cell recognition domain is disclosed to recognize Lewis Y antigen that is expressed by mucosal epithelial cells and the reference also discloses cell recognition domains that bind to mucosal surfaces of any type of cell wherein the cell recognition domain recognizes any eukaryotic receptors (see Cardy et al, page 1, [0005, line 3] and page 2, [0010 "human or

animal subject"]). Cardy et al still inherently anticipate the instantly claimed invention as now claimed.

17. Applicant further traverses the rejection of the claims by Cardy et al, by asserting that "Cardy et al. do not disclose locating the cysteine-cysteine loop of a pathogen in place of amino acid residues 372 to 379, inclusive of SEQ Id NO 2."

18. It is the position of the examiner that the Cardy et al reference locates the epitope loop domain in the location where amino acids 372-379 would be normally placed, and therefore locates the epitope in the same or equivalent location as now claimed. Figure 10 shows the translocation domain, followed by the immunogenic epitope-presenting domain (HIV loop domain), followed by the endoplasmic retention domain. The cell-binding domain is not shown in Figure 10, but would be attached before the translocation domain as shown in the prior figures. Cardy et al still anticipates the instantly claimed invention as now claimed.

1. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

New Grounds of Rejection/Objection
Claim Objections

19. Claims 52-54 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 52 depends from claim 1 and recites the phrase " consisting essentially of" to introduce the four domains of the claimed immunogen. The four domains are

broadly recited and are not limited to the domains recited in claim 1, and is therefore broader in scope than claim 1 from which it depends despite the fact that the claim recites the phrase " consisting essentially of". The phrase " consisting essentially of" permits the presence of additional components or changes in the composition as long as the components do not change the basic and novel characteristics of the composition being claimed. The basic and novel characteristic of claims 1 and 52 is a four domain immunogen that comprises a heterologous immunogen, and claim 52 does not comprise require the epitope presenting domain to be heterologous to the immunogen as recited in claim 1. Additionally, claim 1 recites the terms "comprising" and "having" which are open language claim terms and the phrase " consisting essentially of" can be read as open or partially open. The claim language presented in claim 52 is not internally consistent.

20. Claims 55 and 56 are objected to because of the following informalities:

21. Claim 55 recites the phrase "of pseudomonas exotoxin A"; the word ----Pseudomonas --- should be capitalized.

22. Claim 56 has two periods; it should only have one period at the end of the sentence.

23. Appropriate correction is required.

Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 1-3 provisionally rejected on the ground of nonstatutory double patenting over claims 1, 4,6,11-13, 15,17-20, 42 of copending Application No. 10/432,412 (allowed application). This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The species of non-toxic Pseudomonas exotoxin A-like chimeric immunogen of copending Application 10/ 432,412 comprises a specific species of epitope presenting domain, that is located between domain II and domain III (the location being PE domain Ib), directed to Type IV pilin loop. The instant claimed genus of non-toxic chimeric immunogen of Pseudomonas exotoxin A may comprise any cysteine-cysteine loop of a pathogen and allowed claims 1-7, 11-13, 15, 17-18 of copending Application No. 10/432,412 recite a specific species of immunogen, the immunogen being a Type IV pilin loop sequence. The allowed species of non-toxic Pseudomonas exotoxin A anticipates the instantly claimed

invention as now claimed. Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

26. Claims 1-3, 7-8, 12-13, 47-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

27. Claims 1-3, 7-8, 12-13, 47-55 have been amended to recite the phrase:

"a cell recognition domain of between 10 and 1500 amino acids that binds to an epithelial cell surface receptor on the apical surface of a mucosal membrane of a mammal".

Support for this phrase is cited by Applicant to be found support in Figure 8 and pages 52-53 of the instant Specification.

Upon consideration of the disclosure provided at page 52, the examiner found a **toxic** version of Pseudomonas exotoxin chimera that comprised the V3 loop of MN pg120 to bind to a vitro apical cell surface of Caco-2 cells. The cell culture was suggested that they "**might** predict transport in human large intestinal tissue". The claimed invention is directed to a non-toxic version of PE. The claimed invention is not limited to the V3 loop of pg120, and is also not limited to human Caco-2 cells or human large intestine tissue. This section of page 52 does not

provide original descriptive support for the instantly claimed non-toxic chimeric Pseudomonas exotoxin A.

Upon consideration of disclosure provided at page 53, the examiner found a single non-toxic chimera, with a deletion at position 553 of PE. This species of invention is not claimed. Additionally, the epitope presenting domain at pages 52-53 describe a loop of 26 amino acids, and not the claimed 5 to 350 amino acids in length.

Upon consideration of Figure 8, for support for the newly submitted combination of claim limitations, the examiner found Figure 8 to evaluate an enzymatically active recombinant form of PE which was exposed apically to human Caco-2 cells, and two enzymatically active (toxic) versions of the chimera were described to contain either 14 or 26 amino acids of the V3 loop of HIV-1 MNgp120. This portion of the instant Specification does not provide original descriptive support for a cell recognition domain of 10-1500 amino acids of a non-toxic Pseudomonas exotoxin A that contains an epitope presenting domain of 5 to 350 amino acids in length, because the disclosure does not provide original descriptive support for the instantly claimed genus of non-toxic chimeric immunogens of a Pseudomonas exotoxin A like chimera.

The sections of the Specification to which Applicant has pointed for support for the newly submitted combination of claim limitations exemplified toxic, enzymatically active forms of PE, that only comprised 14 or 26 amino acids within the loop epitope presenting domain.

What is now claimed is directed to a composition that is non-toxic, thus non-enzymatically active chimera, which need not comprise a PE cell recognition domain, the cell recognition domain comprising any sequence of 10 to 1500 amino acids that will recognize a

cell. Additionally, the claimed invention is not limited to exemplified species of apical binding cell recognition domain of PE.

The cell culture of Caco-2 cells described in Figure 8, and pages 52-53 were human cells that were contacted with a toxic form of PE, the cell binding domain being domain 1a, and what is now claimed is a cell recognition domain that will bind to any apical surface of any mucosal mammalian cell of any amino acid sequence within the recited range of amino acids (10-1500 amino acids). A single species of human cell, Caco-2 cell culture, does not provide original descriptive support for the instantly claimed highly variable genus of cell recognition domains of 10-1500 amino acids that will bind to any apical surface of a mucosal membrane in any mammal cell.

Original descriptive support for a genus of sequences that are 10 to 1500 amino acids in length, which are described to evidence the same or equivalent biological activity as PE domain 1a, which in turn will bind to the apical surface of a mucosal cell of any mammal, has not been described. The newly submitted combination of claim limitations does not evidence original descriptive support in the instant Specification. For the reasons set forth above, the claims recite New Matter.

Conclusion

This is a non-final action.

28. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
29. US Pat. 5,328,984 is cited to show domain 1b for substitution of heterologous amino acid sequences into a non-toxic PE Delta 553 (see figure 8 and col. 3, lines 8-18).
30. US006099842A is cited to show a chimeric protein toxin (see all claims).
31. US0006,426,075B1 is cited to show a chimeric PE protein construct.

32. US006498233B1 is cited to show a multidomain protein that comprises a target cell specific binding domain (see claim 1), a translocation domain (see claims 1-2), a endoplasmic reticulum retention domain (see claim 3)
33. US Pat. 6881718 (see pharmaceutical claims) is cited to show a disulfide linked conjugate of PE to an additional protein.
34. US PG-Pub 2004047617 A1 is cited to show a fusion protein that comprises a viral antigen together with PE domains I, II and endoplasmic reticulum retention domain (see claims 1-3, 27-29 and 35).
35. PG Pub 20050079171 A1 is cited to show chimeric immunogens of Pseudomonas exotoxin A.
36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
April 19, 2005

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